of the named inventors of the above-referenced patent application, filed pursuant to 37 C.F.R. § 1.132 in related Application No. 09/526,855. In view of Dr. Kim's declaration and the following remarks, Applicants respectfully request reconsideration of the above-referenced patent application.

a. Rejection Under 35 U.S.C. § 103(a) Over Scholz

Claims 1, 2, 4-7, 15-19, 26 and 27remain rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Scholz (U.S. Patent No. 5,244,886). In citing Scholz, the Office Action alleges that Scholz discloses a generic group of 11-substituted 4,9-dienes and their use as antigestagens. Although the Office Action acknowledges that the instant claims differ from the Scholz reference by reciting specific compounds not exemplified by the prior art, it nonetheless alleges that the claims are obvious because the Scholz reference teaches an equivalence between various substitutents in the 17α-position (*see*, page 3 of the Office Action). Applicants respectfully ***disagree***.

Scholz does ***not*** teach or suggest compounds having the natural trans-anti configuration, *i.e.*, compounds of the present invention. Instead, Scholz discloses compounds having the unnatural syn-anti configuration. In fact, as explained by Dr. Kim in his declaration, a key limitation of Scholz, which is *explicit* in the title, the description, and the claims of the Scholz patent and which distinguishes it from the presently claimed compounds, is that it is directed to a genus of compounds having a steroidal nucleus characterized by a 14-β-H stereocenter (hereinafter C-14) and, thus, the genus of compounds disclosed and claimed by Scholz explicitly ***excludes*** the compounds of the present invention. As pointed out by Dr. Kim, this key limitation is explicitly set forth in the Scholz patent, wherein it is stated:

> As a special feature the compounds of this invention, *deviating from naturally occurring steroids, exhibit a beta-position hydrogen atom on the 14 carbon atom.* Such 14β-H steroids have already recently become known to a limited extent from European patent application 0 277 676.

See, U.S. Patent No. 5,244,886 to Scholz, column 2, lines 54-59 (emphasis added).

In contrast to Scholz, the compounds of the present invention are of the 14-α-H configuration, *i.e.*, the opposite of that in Scholz and, thus, they are not a subgenus of the 14-β-H compounds described in Scholz. As explained by Dr. Kim in his declaration, since 14-α-H is the 'natural' configuration, it is not explicitly indicated in the generic structure of the present application. However, it is supported as being 14-α-H by the naming of compounds throughout the application. In fact, the title of the present application names the compounds of the invention as substituted versions of norpregnadienedione. This is a common name that, in Dr. Kim's opinion, conveys to one of ordinary skill in steroid chemistry that the stereochemistry at C-14 is 14-α-H, the natural configuration: if it were otherwise, that would be an unusual feature that would have to be explicitly indicated in order to be understood. By convention, the stereochemistry of the ring fusion stereocenters of a steroid compound is generally not designated unless it departs from the naturally occurring form. As such, in Dr. Kim's opinion, the 14-α-H stereochemistry of the presently claimed compounds would be readily understood by chemists skilled in steroid chemistry from the generic structure as it is drawn in the original application. It is noted, for example, that even in Scholz, none of the other ring fusion stereocenters is explicitly indicated: only the unnatural one is made explicit with a "wedge bond" in their structures.

Furthermore, as explained by Dr. Kim in his declaration, the ***biological activity*** of a steroid compound is so dependent on the stereochemistry of the ring fusion centers that, to a steroid chemist, it would be unexpected and quite surprising for the biological activity of a 14-β-H compound to resemble that of an otherwise identical 14-α-H compound. As explained by Dr. Kim, the stereochemistry at these centers has a dramatic effect on the molecular shape which is expected by those of skill in the art to dramatically alter biological activity. In Dr. Kim's opinion, the biological activity of a

14-β-H compound would ***not*** motivate one to synthesize corresponding 14-α-H compounds.

Similarly, as explained by Dr. Kim in his declaration, the ***chemical reactivity*** of a steroid compound is so dependent on the stereochemistry of the ring fusion centers that, to a steroid chemist, it would be unexpected and quite surprising for the reactivity of a 14-β-H compound to resemble that of an otherwise identical 14-α-H compound. The stereochemistry at these centers has a dramatic effect on the molecular shape which, in Dr. Kim's opinion, is expected to dramatically alter reactivity. As such, it is Dr. Kim's opinion that the synthetic transformations of a 14-β-H compound would not be useful to predict how a corresponding 14-α-H compound would react and, thus, the synthetic methods taught by Scholz for 14-β-H compounds would not be expected to enable one to synthesize corresponding 14-α-H compounds.

In view of the foregoing remarks and the declaration of Dr. Kim, claims 1, 2, 4-7, 15-19, 26 and 27 are non-obvious and, thus, patentable over Scholz. Accordingly, Applicants urge the Examiner to withdraw the obviousness rejection over Scholz.

b. Rejection Under 35 U.S.C. § 103(a) Over Peeters

Claims 1, 2, 4-7, 15-19, 26 and 27 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Peeters (U.S. Patent No. 5,741,787). In maintaining this rejection, the Office Action alleges that Peeters discloses a generic group of 11-substituted steroids. Although the Office Action acknowledges that the instant claims differ from the Peeters reference by reciting specific compounds not exemplified by the prior art, it nonetheless alleges that the claims are obvious because the Peeters reference teaches an equivalence between various substitutents in the 17α-position (*see*, page 3 of the Office Action). Applicants respectfully ***disagree***.

As explained by Dr. Kim in his declaration, the compounds that Peeters exemplifies and enables ***differ*** from the present invention in the stereochemistry at C-17.

Except for a single *intermediate*, the compounds described in Peeters all have a hydroxyl group as R5 on the Peeters generic, *i.e.*, a β-hydroxy substituent. That intermediate (*see*, Example 5(b)-(c) in Peeters, at column 7, lines 56-62) lacks a second substituent at C-17, and further lacks the C-3 carbonyl of the present invention. The carbonyl on the A-ring in that compound is also protected as a dioxolane acetal; thus, according to Dr. Kim, that intermediate is ***not*** analogous to the claimed compounds of the present invention. As set forth by Dr. Kim, in every compound described in Peeters that contains both a hydroxyl and another substituent at C-17, the hydroxyl is *β, i.e.*, it is the R5 substituent, whereas the β substituent in the present invention is necessarily an acyl group, and a hydroxyl or other group in the claimed compounds can only be α. Clearly, the compounds exemplified by Peeters have the ***opposite*** (or inverted) stereochemistry at C-17 from the claimed compounds.

Moreover, as pointed out by Dr. Kim in his declaration, the scope of the examples in Peeters is extremely narrow: the overall teaching offers very limited direction to one motivated to synthesize antiglucocorticoid compounds substantially different from the few described. The ***six*** novel compounds named and tested are all 17-β-hydroxy-17-α-alkynes. It is not apparent, in Dr. Kim's opinion, that one of skill in the art would foresee a "reasonable expectation of success" from such limited precedent in the synthesis of compounds where (a) the stereochemistry at C-17 is inverted, (b) an sp^2 carbon substituent is incorporated at C-17 in place of the sp-hybridized carbon of the alkyne group, and (c) a heteroatom (the carbonyl oxygen of the acyl group in the present invention) is introduced at the R5 substituent, ***simultaneously*** changing three features that were conserved in ***each*** of the compounds shown to possess the activity of interest in Peeters.

Further, it is Dr. Kim's opinion that Peeters does not provide motivation to synthesize the compounds of the present invention. Peeters' preferred embodiments specify "R_4 is prop-1-ynyl, R_5 is hydroxy" (*see*, Peeters, column 2 at line 53), which gives the opposite stereochemistry at C-17 from compounds that would be analogous to

the compounds of the present invention. Other than including a generalized acyl group in a list of substituents that *could* be used for R5, and similarly including hydroxy in an array of substituents to be considered for R4, it gives no indication which substituents stand out aside from that preferred embodiment description. Since the preferred compounds have the opposite (or inverted) stereochemistry from compounds analogous to those of the present invention, what little direction Peeters does provide ***teaches away*** from analogs that would render the present invention obvious, in Dr. Kim's opinion, by teaching that the activity is associated with the opposite stereochemistry at C-17.

As pointed out by Dr. Kim, Tables 1 and 2 of the present application provide activity data showing the relative antiglucocorticoid and antiprogestational activities of selected compounds. In Dr. Kim's opinion, this data is surprising because it demonstrates that the antiglucocorticoid activity can be substantially separated from antiprogestational activity with the compounds of the present invention. In Peeters, the compounds possess very substantial antiglucocorticoid activity. In contrast, the compounds of the present invention possess antiprogestational activity, with substantially less antiglucocorticoid activity. In Dr. Kim's opinion, this is a highly significant separation of properties, because the reduced antiglucocorticoid activity greatly enhances the clinical potential for extended therapeutic applications.

Furthermore, as explained by Dr. Kim, Peeters only provides one synthesis route to create the stereochemistry at C-17 (*see*, Example 5(d), column 8 at lines 7-21 of the Peeters patent). This synthesis route involves the addition of acetylene to a ketone at C-17 and, based on the yields reported, it produces ***quantitatively*** the *beta*-hydroxy product. According to Dr. Kim's calculations, which are set forth in his declaration, there is no indication that the other isomer, which *might* be useful to prepare compounds of the present invention, was produced, and no other method to create a chiral tertiary alcohol center at C-17 is taught. All other examples in Peeters directed to the synthesis of compounds with a carbon-based substituent at C-17 begin with the *beta*-hydroxy in the R5 position of the Peeters generic compound. Some involve modification

of the acetylenic group, but in Dr. Kim's opinion, none provides a way to invert that center or to introduce an acyl substituent at C-17.

In fact, as explained by Dr. Kim in his declaration, their attempts to functionalize an acyl group at C-17 in the presence of the 11-β-dimethylaminophenyl group, which is a preferred substituent in the compounds of the present invention, demethylation of the dimethylamino group rather than the desired functionalization of the acyl group was observed. This finding has been published by Dr. Kim in *J. Chem. Soc. Chem. Commun.*1985-86 (1994), a copy of which is attached to his declaration as Exhibit B. According to Dr. Kim, preparation of the claimed compounds required that a new synthetic route be developed. As such, according to Dr. Kim, Peeters does not enable the synthesis of compounds of the present invention by one of ordinary skill in the art.

In view of the foregoing remarks and the declaration of Dr. Kim, claims 1, 2, 4-7, 15-19, 26 and 27 are non-obvious and, thus, patentable over Peeters. Accordingly, Applicants urge the Examiner to withdraw the obviousness rejection under 35 U.S.C. § 103 over Peeters.

c. ***Rejection Under 35 U.S.C. § 103(a) Over Torelli***

Claims 1, 2, 4-7, 15-19, 26 and 27 remain rejected under 35 U.S.C. § 103 as allegedly being obvious over Torelli. In maintaining this rejection, the Office Action alleges that although the instant invention differs from the Torelli reference by reciting compounds ***not*** exemplified by this reference, Torelli teaches an equivalence between various substitutents (*see*, pages 2-3 of the Office Action mailed November 5, 2001). Applicants respectfully ***disagree***.

As previously explained, the only compound disclosed by Torelli that arguably falls within the scope of the claim 1, as originally filed, is compound 10, which is recited at columns 15 and 16 of the Torelli patent. This is true despite the fact that Torelli discloses pages upon pages of compounds. Again, compound 10 is used in the present invention as an ***intermediate*** to form the other compounds of interest. Moreover, it is again pointed out that compound 10 has been explicitly excluded from amended

claim 1. The remaining Torelli compounds are ***structurally different*** from the compounds recited in amended claim 1.

In addition to being ***structurally different*** from the claimed compounds, the Torelli compounds are ***functionally different*** from the claimed compounds. More particularly, as explained in the specification, one of the advantages of the compounds of the present invention (*i.e.*, the compounds of Formula I) is that they possess potent antiprogestational activity with minimal antiglucocorticoid activity (*see*, the specification at, for example, page 1, lines 2-5; page 2, lines 19-20; and page 20, lines 20-21). In contrast to the compounds of the present invention, Torelli explicitly states that the compounds disclosed therein have "remarkable antiglucocorticoid properties" (*see*, *e.g.*, column 38, lines 55-57 of Torelli).

As explained above, Dr. Kim, in his declaration, pointed out that Tables 1 and 2 of the present application provide activity data showing the relative antiglucocorticoid and antiprogestational activities of selected compounds. In Dr. Kim's opinion, this data is surprising because it demonstrates that the antiglucocorticoid activity can be substantially separated from antiprogestational activity with the compounds of the present invention. As with the Peeters' compounds, the Torelli compounds possess very substantial antiglucocorticoid activity. In stark contrast, the compounds of the present invention possess antiprogestational activity, with substantially less antiglucocorticoid activity. In Dr. Kim's opinion, this is a highly significant separation of properties, because the reduced antiglucocorticoid activity greatly enhances the clinical potential for extended therapeutic applications.

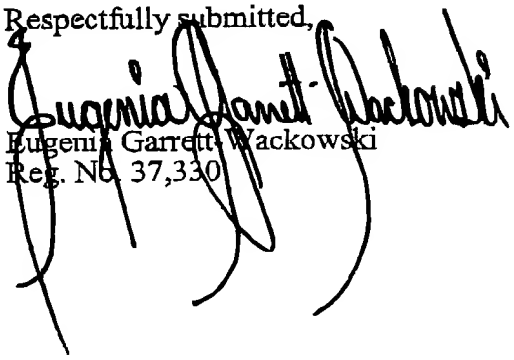
In view of the foregoing, it is readily apparent that the Torelli compounds are both structurally and functionally different from the claimed compounds. In view of such structural and functional differences, the claimed compounds are nonobvious and, thus, patentable over Torelli. Accordingly, Applicants urge the Examiner to withdraw the rejection of claims 1, 2, 4-7, 15-19, 26 and 27 under 35 U.S.C. § 103(a) over Torelli.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
EGW:lls

WC 9045029 v1